CHAPTER 14

Confusion

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Confusion, the impairment of higher thought processes, can be caused by a variety of illnesses, trauma, or medications. Confusion is one of the most common complaints encountered by family physicians, especially among their older adult patients. A symptomatic approach involving history, examination, and judicious use of laboratory and imaging will allow the clinician to provide optimal care for patients presenting with confusion.

DEMENTIA

Dementia is the syndrome of chronic and progressive impairment of memory and at least one other cognitive domain, resulting in decreased functional skills and impairments in social or occupational function, which does not occur only during delirium (delirium is acute with a specific "organic" cause requiring specific treatment). The vast majority of dementia is not reversible, but all treatment goals in dementia are to maintain independence, relieve patient suffering, and decrease caregiver burden, for as long as possible.

The DSM-IV-TR diagnostic criteria for Alzheimer's disease (AD) are presented in Table 14-1. AD is the most common form of dementia, followed by mixed-cause dementia (AD and vascular), vascular dementia, dementia with Lewy bodies, and Parkinson's disease with dementia (Table 14-2). "Reversible dementias," are better described as "potentially reversible," due to the low proportion who fully regain cognitive function.

Symptoms vary widely among individuals, disease stage, and type of dementia. It is important to corroborate patient history with another source. Symptoms can be classified as cognitive or behavioral.

Symptoms

- Difficulty forming new memories +++++
- Trouble recalling recent events, conversations, or objects +++++
- Difficulty recalling names of familiar people or objects
- Frequent use of imprecise terms in place of object names (calling a broom a "stick" or "a thing to sweep with")
- Map reading
- Difficulty discerning visual boundaries in the environment
- Managing financial affairs

- Planning meals, organizing shopping or excursions
- Driving
- Aggression, verbal or physical
- Repetitive vocalization or verbalization
- Delusions, often with paranoid content
- Hallucinations (seen early in dementia with Lewy bodies)
- Wandering or pacing
- Apathy and depressed affect
- Sleep cycle disturbances

Table 14-1. Alzheimer's Disease Diagnosis by DSM-IV-TR

1. Multiple cognitive impairments in both:
   - Memory impairment (difficulty learning new information or recall of previously learned information)
   - One or more of the following: aphasia, apraxia, agnosia, impaired executive functioning (planning, organizing, sequencing, and abstracting)
2. These disturbances result in significant occupational and/or social impairment and are a significant decline from prior function.
3. Gradual onset and progressive cognitive decline
4. Not due to other central nervous system, systemic, or substance-induced diseases known to cause dementia (cardiovascular disease; Parkinson's disease; Huntington's disease; subdural hematoma; normal pressure hydrocephalus; brain tumor; hypothyroidism; B_{12}, folic acid, or niacin deficiency; hypercalcemia; human immunodeficiency virus; or neurosyphilis)
5. Impairments do not occur exclusively during delirium.
6. Impairments not better accounted for by psychiatric disorders such as major depression or schizophrenia

Table 14-2. Dementias Types

DEMENTIA	SIGNS AND SYMPTOMS
Alzheimer's disease	Progressive course, prominent memory loss, language, executive functioning with symmetric neurologic examination
Vascular dementia	Asymmetric neurologic examination, risk factors or history of stroke (overlaps with Alzheimer's disease because both are common)
Dementia with Lewy bodies	Dementia with two out of three of the following: parkinsonism, fluctuating cognition, well-formed visual hallucinations. 50% have severe neuroleptic sensitivity. Some have rapid eye movement sleep behavior disorder.
Parkinson's disease with dementia	Parkinson's disease diagnosis precedes dementia by at least 1 year.
Frontotemporal dementia	Disinhibition, social inappropriateness, apathy and/or language problems worse than memory or visuospatial impairment. Onset usually before age 65.

Signs

- Neurologic examination
  - Physical examination findings depend on the stage and type of dementia.
  - In early AD the peripheral and cranial nerve examination is normal. Abnormal neurologic examination findings should prompt evaluation for conditions other than AD.
  - Parkinsonism is present in both Lewy body dementia and Parkinson's disease with dementia.
  - Myoclonus and seizures may be seen in advanced dementia.
  - Gait difficulties and urinary incontinence exist commonly in an older adult, but if newly associated with an early dementia, should raise suspicion of normal pressure hydrocephalus.
- Cognitive testing
  - The Mini-Mental State Examination (MMSE) identifies cognitive impairment in multiple domains on a 30-point scale, is used to screen for disease as well as follow disease progress over time, and takes about 10 minutes to perform. Scores less than 24 suggest cognitive impairment, but scores of 24 or more do not exclude impairment. It is relatively insensitive in early AD and shows little change with disease progression in severe AD. Educational level affects results.
  - The Mini-Cog is a 3-minute test that identifies people who need further evaluation and is relatively unbiased by education and literacy. It consists of asking the patient to register three unrelated words, followed by the Clock Drawing Test (correct placement of numbers, then hands, indicating "11:10"), then testing for uncued recall of the three words. Each word recalled yields 1 point. A normal clock drawing yields 2 points, and an abnormal clock yields 0 points. Mini-Cog scores of 0 to 2 suggest possible dementia; scores of 3 to 5 suggest no dementia.

Workup

- Blood tests to screen for comorbid conditions common in patients with suspected dementia and possible reversible causes. Syphilis and/or HIV serologic testing if high pretest probability, otherwise evidence does not strongly support routine testing
  - Complete blood cell count (CBC)
  - Electrolytes
  - Glucose
  - Folate
  - Vitamin B_{12}
  - Thyroid function
- Imaging
  - Structural neuroimaging
    - Noncontrast head CT to identify brain tumors, subdural hematoma, and normal pressure hydrocephalus (NPH) (rare)
    - Consider MRI, depending on availability, and if physical examination or risk factors suggest cerebrovascular disease.

- Functional neuroimaging
  - Single photon emission tomography (SPECT) and positron emission tomography (PET) imaging may add predictive value to the clinical diagnosis of AD, distinguishing AD from minimal cognitive impairment (MCI), and other dementias, but its routine use is not recommended at present.
- Consultation or referral considerations
  - Onset before 65 years of age
  - Behavior symptoms early or severe behavioral problems
  - Rapid course of disease (weeks to months rather than years)
  - Concerns about driving safety or independent living
  - Questions about functional neuroimaging (SPECT and PET), genetic testing, neuropsychologic testing, or genetic testing
  - Distinguishing dementia from MCI, depression, and uncommon secondary causes
- Staging
  - Use the MMSE score as follows:
    - Mild dementia: 18 to 23
    - Moderate dementia: 11 to 17
    - Severe dementia: 10 or less
    - MMSE scores decline on average about 3 points per year in AD, with a range of 0 to 6 points per year.
  - The Functional Assessment Staging Test (FAST)
    - 16-item scale reflecting the progressive functional losses of AD (Table 14-3)
    - FAST is easily understood by patients and caregivers.
    - Helps plan for future needs

Comments and Treatment Considerations

Avoid alcohol and smoking, control vascular risk factors, and encourage regular physical and mental activity. Identify drugs with anticholinergic properties and discontinue whenever possible. Vitamin E shows conflicting evidence for outcomes in AD, and is associated with increased cardiovascular mortality, so is not recommended routinely. Ginkgo biloba is not available in standardized formulations, so is not routinely recommended.

Some patients with mild to moderate AD show modest improvement in measures of cognition and function using the acetylcholinesterase inhibitors (donepezil, rivastigmine, and galantamine; Table 14-4). There is no conclusive evidence of efficacy for behavioral and neuropsychiatric symptoms in AD.

As a class these drugs commonly cause GI cholinergic side effects, such as nausea, anorexia, vomiting, and diarrhea, which may lead to weight loss. Tolerance often develops to the GI side effects. Some patients tolerate one acetylcholinesterase inhibitor better than another.

Cognition, behavior, and function (activities of daily living [ADL] and instrumental activities of daily living [IADL]) should be monitored at regular intervals (every 3 to 6 months). Continuation of the drug should be questioned if there is significant decline in MMSE and ADL 6 months after initiation of therapy, or when the patient reaches severe stage dementia (MMSE less than 10 and full ADL dependency).

Table 14-3. Functional Assessment Staging Test

FAST STAGE	FUNCTIONAL ASSESSMENT
1	No difficulties, either subjectively or objectively
2	Complains of forgetting location of objects; subjective work difficulties
3	Decreased job functioning evident to coworkers; difficulty in traveling to new locations
4	Decreased ability to perform complex tasks (e.g., planning dinner for guests; handling finances; marketing)
5	Requires assistance in choosing proper clothing
6a	Difficulty putting clothing on properly.
6b	Unable to bathe properly; may develop fear of bathing
6c	Inability to handle mechanics of toileting (i.e., forgets to flush; doesn't wipe properly)
6d	Urinary incontinence
6e	Fecal incontinence
7a	Ability to speak limited (1-5 words a day)
7b	All intelligible vocabulary lost
7c	Nonambulatory
7d	Unable to sit up independently
7e	Unable to smile
7f	Unable to hold head up

The functional staging score is highest ordinal value. Ignore item if assessed as being due to other causes apart from dementia.

Memantine has FDA approval for moderate dementia in AD. Memantine may be used alone, or in combination for patients already taking an acetylcholinesterase inhibitor. Side effects include dizziness, and less commonly confusion and hallucinations.

Caregivers should be monitored for stress and encouraged to gain support and education through their local Alzheimer's Association (1-800-272-3900 or www.alz.org). Adult daycare, respite care, and nursing home options should be discussed at the appropriate disease stages.

Patients should address choice of durable power of attorney for health care and other matters, as well as advance directives for end-of-life care while decision-making capacity is preserved.

Home safety is tied to availability of skilled caregivers and physical design of the home space. Use of the stove and other dangerous appliances and tools, cigarettes, and fireplace should be assessed at regular intervals. People with dementia who are at risk

Table 14-4. Medications for Alzheimer Disease

DRUG	CLASS	DOSE RANGE (MINIMUM THERAPEUTIC TO TARGET DOSE)	TITRATION SCHEDULE
Donepezil	Acetylcholine-sterase inhibitor	5-10 mg daily	5 mg at bedtime daily; increase to 10 mg daily after 6 weeks
Rivastigmine	Acetylcholin-esterase inhibitor	3-6 mg twice daily	1.5 mg twice daily, every 2 weeks; increase individual dose by 1.5 mg
Galantamine	Acetylcholin-esterase inhibitor	8-12 mg twice daily	4 mg twice daily; every 4 weeks increase individual dose by 4 mg
Memantine	NMDA receptor antagonist	10 mg twice daily	5 mg daily for >1 week; then increase total daily dose by 5 mg daily (divide dose twice daily), to 10 mg twice daily

for elopement should have an identification bracelet or necklace (such as Alzheimer's Association Safe Return Program) in addition to the appropriate level of supervision.

Plan for alternative transportation from the time of dementia diagnosis. Practice guideline recommendations for driving with mild dementia range from giving advice about impairment and increased risks to advising that all people with mild dementia must stop driving. Physicians should know local legal reporting requirements for dementia and options for older driver evaluation as described in the AMA/National Highway Traffic Safety Administration (NHTSA) guide.

Most people with dementia experience behavioral and neuropsychiatric symptoms. Disturbing delusions, hallucinations, and aggression symptoms increase caregiver burden and patient suffering. An organized approach is recommended, which is individualized, based on behavior type and severity, the type of underlying dementia, and patient-caregiver dynamics as follows:

- Step 1: Identify the nature of the behavior, provocatory factors, and effect of the behavior on patient and caregiver.
- Step 2: Review medication list and eliminate nonessential drugs and those with anticholinergic properties.
- Step 3: Evaluate and treat any pain symptoms and delirium (search for medication side effects, infection, systemic illness, superimposed CNS disease, bowel impaction, urinary retention).

- Step 4: Evaluate and treat any depression and anxiety (consider that pacing and repeated vocalizations may be mood symptoms, especially in dementia patients with language problems).
- Step 5: Conduct an environmental assessment, implement interventions, and provide caregiver education and support.
- Step 6: Consider starting a cholinesterase inhibitor in patients with mild to moderate AD.
- Step 7: Start an antipsychotic drug if the above interventions are ineffective, and the symptom is judged sufficiently threatening to safety and well-being of the patient or caregiver. Identify a target behavior symptom (e.g., physical aggression), goal for treatment, and time frame to attain improvement, then obtain informed consent regarding risks. Use the lowest dose of an atypical antipsychotic drug and monitor for side effects (especially sedation and extrapyramidal signs). Antipsychotic drug dose reduction should be attempted at least every 6 months. Atypical antipsychotic drugs have variable and modest effects on neuropsychiatric symptoms. The FDA has determined that atypical antipsychotic drugs are associated with increased mortality in the treatment of behavioral disturbances in older adults with dementia. Patients with Parkinson's disease and dementia can develop worsened movement disorder from typical or first-generation antipsychotic drugs (better tolerance is noted with atypical drugs, such as quetiapine). In Lewy body dementia, 50% of patients show severe neuroleptic sensitivity (worsened extrapyramidal symptoms, orthostasis, decreased level of consciousness), and first-generation antipsychotic drugs should be avoided.

Medicare guidelines for hospice referral require physician certification that life expectancy is 6 months or less, often interpreted as FAST stage 7a or higher, plus a major comorbid illness in the past 12 months.

The USPSTF states there is insufficient evidence for or against routine screening for dementia when it is not suspected by clinical presentation. Advocates of dementia screening emphasize the value of early diagnosis for planning future needs for support services.

Serum apolipoprotein E and cerebrospinal fluid (CSF) tau markers are not recommended for routine use. The results are often complex to interpret and have ethical/insurability issues requiring informed consent.

MEMORY LOSS WITHOUT DEMENTIA

People with MCI have memory problems but are not demented and are living independently. They may be experiencing memory loss without dementia. MCI is a heterogeneous group of people whose memory problems are stable, reversible, or in transition to dementia. About 6% to 25% of 65- to 89-year-olds with MCI will develop dementia per year, compared with 1% to 4% per year for similar-aged patients without MCI.

Symptoms
- Similar to early dementia memory complaints
- Do not affect ADL performance
- Subjective memory complaints, ideally confirmed by an informant ++++
- Fully independent in all ADL ++++

Signs
- Abnormal objective cognitive testing ++++
- Normal cognitive function in other domains besides memory ++++
- MMSE scores less than 24 ++++
- MMSE scores greater than or equal to 24, with further evaluation such as serial cognitive screening tests, or referral for neuropsychologic testing to confirm no physical examination abnormalities ++++
- Do not meet diagnostic criteria for dementia ++++

Workup
- Depression and sleep apnea can cause reversible memory problems. Referral for neuropsychologic testing can be useful in distinguishing normal memory from MCI and depression.
- Laboratory and imaging tests are not useful to distinguish MCI from normal or dementia, but may be applied to patients with MCI to detect underlying conditions that might cause mild cognitive problems, depending on clinical circumstances.

Comments and Treatment Considerations
Patients with MCI should be followed for development of dementia. There is no evidence to support use of vitamin E, cholinesterase inhibitors, or memantine in patients with MCI to prevent development of dementia.

DELIRIUM

Patients with delirium present acutely (hours to days) with a fluctuating course of disturbed cognition, attention, perception, and/or reduced awareness of their environment. Delirium is a syndrome associated with medical illness; therefore, its recognition should prompt a search for an underlying cause. Conditions requiring rapid diagnosis and treatment, such as hypoxia, hypoglycemia, encephalitis, and other infections should be considered.

Delirium is common, associated with high morbidity and mortality, and contributes to prolonged hospital length of stay. Poor rehabilitation and complications such as pneumonia and decubiti are often the result.

Delirium is classified as hyperactive, hypoactive, and mixed types. Psychomotor agitation is the hallmark of the hyperactive type, whereas the hypoactive type presents with lethargy or apathy. The mixed type has both hyperactive and hypoactive features. The gold standard diagnostic criteria for delirium are defined by DSM-IV-TR (Table 14-5). The Confusion Assessment Method (CAM) is a validated bedside tool (Table 14-6) that can be completed in 5 minutes and accurately diagnoses delirium.

Table 14-5. DSM-IV-TR Criteria for Delirium

- Disturbance of consciousness (i.e., reduced clarity of awareness about the environment) with reduced ability to focus, sustain, or shift attention
- A change in cognition (e.g., memory deficit, disorientation, language disturbance) or development of a perceptual disturbance that is not better accounted for by a preexisting, established, or evolving dementia
- The disturbance develops over a short period of time (usually hours to days) and tends to fluctuate during the course of a day.
- Evidence from the history, physical examination, or laboratory findings indicates that the disturbance is caused by a direct physiologic consequences of a general medical condition.

From *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition, Washington, DC, 2000, American Psychiatric Association.

Table 14-6. Confusion Assessment Method (CAM) for Delirium Diagnosis

The diagnosis of delirium requires the presence or abnormal rating for the features (1) and (2), and either (3) or (4).

FEATURE	DELIRIUM DIAGNOSIS	CONFUSION ASSESSMENT METHOD
1	Acute onset and fluctuating course	Is there evidence of an acute change in mental status from the patient's baseline? Did this behavior fluctuate during the past day, i.e., tend to come and go or increase and decrease in severity?
2	Inattention	Does the patient have difficulty focusing attention, e.g., being easily distractible or having difficulty keeping track of what was being said?
3	Disorganized thinking	Is the patient's speech disorganized or incoherent, such as rambling or irrelevant conversation, unclear or illogical flow of ideas, or unpredictable switching from subject to subject?
4	Altered level of consciousness	This feature is shown by any answer other than "alert" to the following question: Overall, how would you rate this patient's level of consciousness?

Alert (normal), vigilant (hyperalert), lethargic (drowsy), stuporous (difficult to arouse), or comatose (unarousable)

From Inouye SK, van Dyck CH, Alessi C, et al: Clarifying confusion: the confusion assessment method, *Ann Intern Med* 113:941-948, 1990.

Symptoms

- High individual variability within a single episode
- Clouding of consciousness
- Decreased awareness of the environment
- Sleep cycle disturbances range from mild insomnia or excessive daytime sleepiness to severe nocturnal agitation and confusion
- Perceptual disturbances (illusions and hallucinations) are usually visual
- Delusions with paranoid features
- Difficulty following the direction of conversations
- Impaired orientation
- Difficulty with multistep commands

Signs

- Reverse spelling of words or sequences, such as spelling one's name or a familiar word backward
- Repeating in reverse order the days of the week or months of the year
- Counting backward from 20
- The Serial Seven Subtraction Test
- Digit-span testing
- Tests of cognition such as the Mini-Cog or MMSE are usually abnormal.
- Because delirium can complicate a preexisting dementia (diagnosed or not), subsequent serial testing to document cognition resolution or baseline is valuable.
- Focal neurologic examination findings may or may not be present. Any abnormality, if present, should provoke an evaluation for underlying neurologic disease; likewise, abnormalities in vital signs and general physical examination, if present, should prompt evaluation.

Workup

- Check oxygen saturation and blood glucose.
- Obtain a complete medical history.
- Interview secondary sources about prior level of cognition and function, recent illness, ingestions, trauma, and review the medication list, with close attention to new medications and those with anticholinergic properties.
- Perform a complete physical and neurologic examination.
- Cognitive testing: Mini-Cog or MMSE, tests of attentional ability such as reverse order word sequences or digit span
- Basic laboratory tests are urinalysis, electrolytes, glucose, liver function tests, CBCD, TSH, ECG, chest x-ray, pulse oximetry, or arterial blood gas.
- Additional laboratory tests: Depending on individual presentation, history, and physical examination signs, consider serum and urine toxicology, rapid plasma reagin (RPR) or Venereal Disease Research Laboratory (VDRL), heavy metal screen, vitamin B_{12} and folate, ANA, urine porphyrins, ammonia, HIV; drug levels (digoxin, lithium, theophylline, phenobarbital, cyclosporine).
- CT or MRI of the head, or EEG if concern for seizures
- Lumbar puncture when there is concern for CNS infection

Comments and Treatment Considerations

There are two primary goals of treatment for delirium. First, identify and treat the underlying cause. Review the medication list for adverse drug effects, anticholinergic drugs, and drug interactions. Eliminate any offending agents. Seek early diagnosis of serious, underlying medical illness, which include:

- Infections (urinary tract, pneumonia, CNS)
- Electrolyte imbalance (dehydration, hyper- and hypoglycemia)
- Acute coronary syndromes
- Acute stroke (rare cause)
- Hypoxia
- Hyper- or hypothermia
- Noninfectious encephalopathy: hypertensive/Wernicke's, liver failure, other
- Ethyl alcohol (ETOH) or drug intoxications and withdrawal syndromes

Second, relieve distress and ensure safety of both patient and caregiver from the cognitive and behavioral effects of the delirium. Delirium can impair cognition and perceptions to a degree that patients are unable to safely care for themselves and may pose a danger to themselves and others. Decisional capacity is variably affected. It may be preserved partially, intermittently, or globally impaired. Physicians should be familiar with the patient's advanced directives and local law as it relates to emergency treatment and surrogate decision making.

Patients need to be assessed for suicide risk, falls, and elopement. Medically nonessential lines should be removed. Physical restraints can increase agitation and risk for entrapment or asphyxia injuries. Continuous presence of a professional sitter is the preferred means for dealing with agitation. If physical restraints are used, documentation of indication and periodic reassessment of need is required.

Orient to time and place with wall clocks, calendars, and gentle reminders by staff; familiar pictures or objects may help reduce anxiety. Reduce noise and excess stimuli as much as possible. Windows and natural light sequences may help lessen disorientation; individuals whose symptoms worsen at night may benefit from improved lighting. Ensure use of hearing aids and eyeglasses. Engage the patient in physical activity as early as possible with therapies and nursing.

Antipsychotic medications may be required to improve patient safety and reduce distress until the underlying cause is fully treated. Of the antipsychotic medications, haloperidol has the most extensive record of use. The general dictum is to start with low doses, maintain an effective dose for several days (typically 2 to 3 days), then taper down the dose and discontinue. In older adults, haloperidol doses as low as 0.25 to 0.5 mg twice daily, and every 4 hours as needed, may be effective. In younger adults, haloperidol doses of 1 to 2 mg twice daily and every 2 to 4 hours as needed are used. Higher doses are used in more agitated patients. Benzodiazepine use is not recommended except for alcohol or benzodiazepine withdrawal.

POINTS OF INTEREST

- Vulnerable state and precipitating event: the more vulnerable the brain, the less of a precipitating event is needed to cause delirium.
- Pathophysiology of the vulnerable brain is believed related to cholinergic deficiency state, and therefore those individuals with dementia are more vulnerable to developing delirium.
- Duration of delirium and associated cognitive impairment may last weeks to months from the time of a precipitating event and some feel there is never a complete return to baseline, pointing to the need for primary prevention.
- Hospitalization and surgery, particularly hip surgery, portends a greater risk for development of delirium.

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